Health Effects of Marijuana Use

Nassima Aitdaoud Tiouririne M.D
Associate Professor
University of Virginia

Terminology

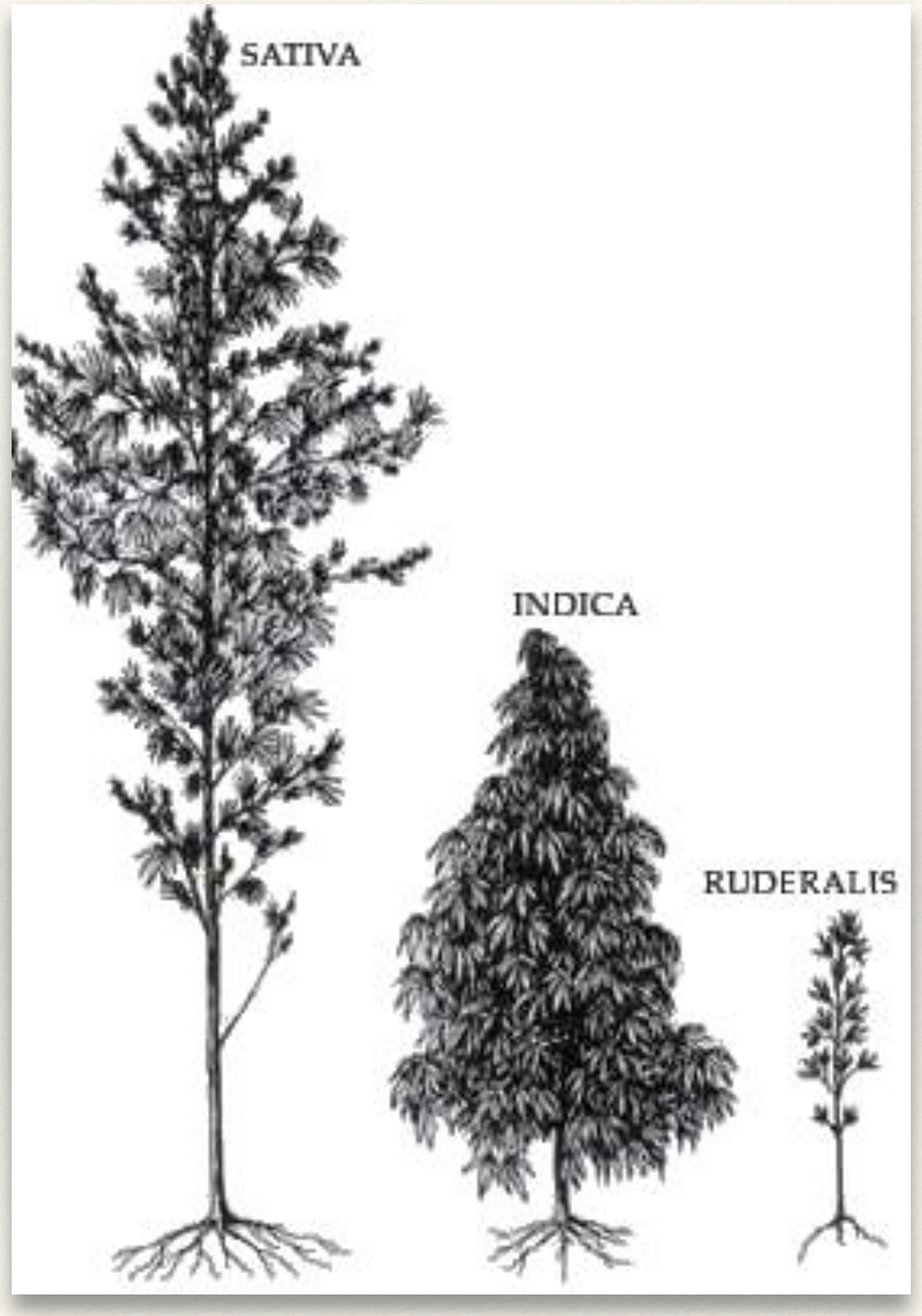
Cannabis vs Marijuana

folk etymology: “Marijuana” = “Maria” + “Juana”

“cannabis” or “hemp” used prior to adoption of Mexican Spanish “marihuana” in early 1900s

Nahautl word “mallihuan” meaning “prisoner”

The agreed international term is ‘cannabis’



What is Marijuana?

- Commonly known as *pot, grass, reefer, weed, herb, Mary Jane*, or *MJ.* It is a greenish-gray mixture of the dried, shredded leaves, stems, seeds, and flowers of *Cannabis sativa.*
- Used most commonly in hand-rolled called *Joints*.
- Pipes or water pipes called *bongs*.
- Marijuana cigars, or *blunts*.
- Also is used to brew tea
- Sometimes is mixed into foods.

Marijuana Components

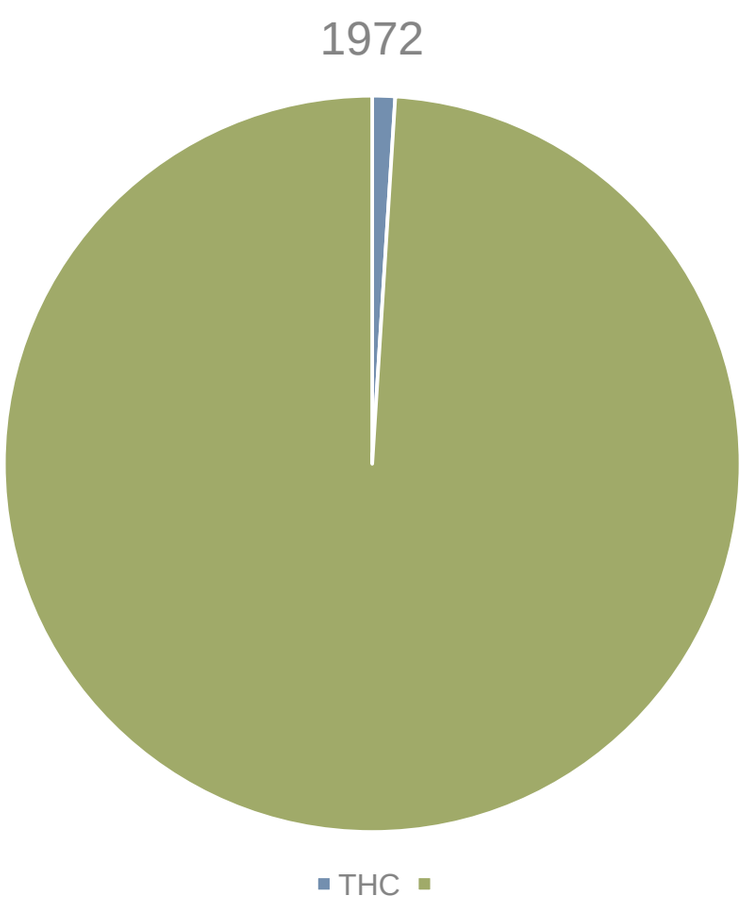
- **480** natural components found within the Cannabis sativa plant, of which **66** have been classified as "cannabinoids
- **delta-9-tetrahydrocannabinol (Δ9-THC):** psychoactive effects of cannabis
- The different subclasses are:
  - Cannabigerols (CBG)
  - Cannabichromenes (CBC)
  - Cannabidiols (CBD);
  - Tetrahydrocannabinols (THC)
  - Cannabinol (CBN) and cannabinodiol (CBDL)
  - Other cannabinoids (such as cannabicyclol (CBL), cannabielsoin (CBE), cannabitriol (CBT) and other miscellaneous types).

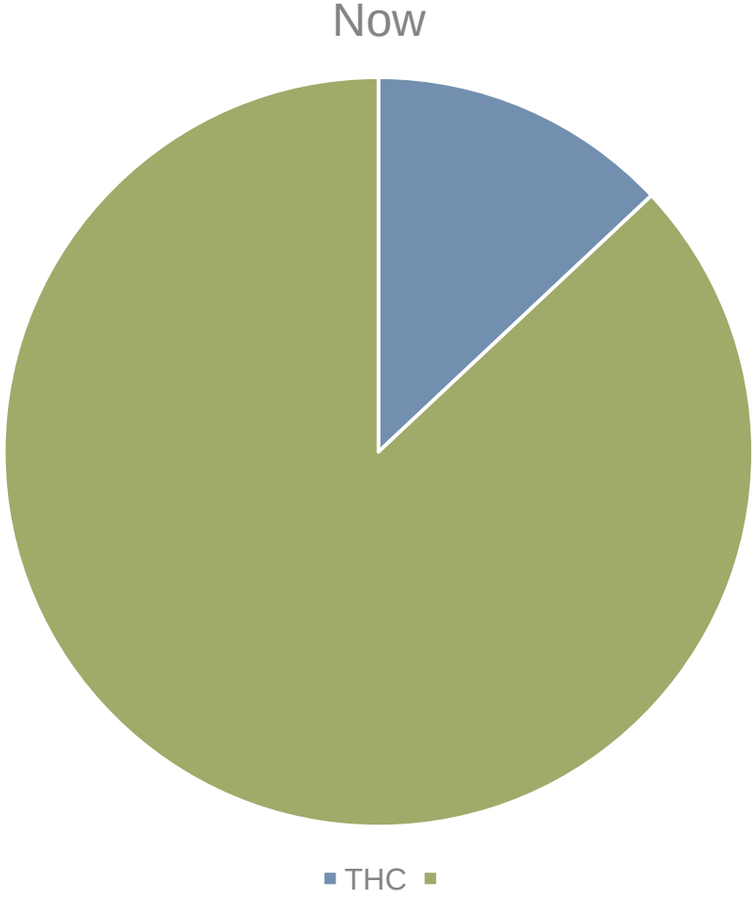
Difference Between Cannabinoids

- CBG, CBC and CBD no psychoactive effect
- **THC, CBN, CBDL** are psychologically active to varying degrees
- **CBD is the most abundant (40% of cannabis resin).**
- CBD may actually have anti-anxiety effects and lessen the psychoactive effects of THC.
- Concentration of THC in marijuana has varied across the years

Potency

- THC is indicative of potency and the concentration of THC has markedly increased over the years (1% to 13% now)





Recently Tested Medical Marijuana Strains

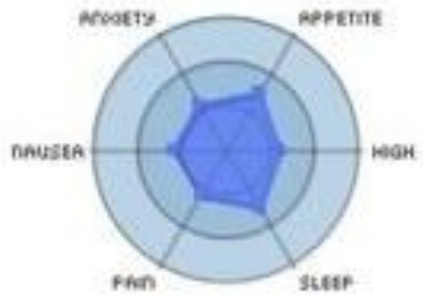
Gorilla Purple

Kern River Collective

THC: 10.41%
CBD: 0.52%
CBN: 0.87%

2 weeks ago

BudGenius Strain ID: BG0010001E81A



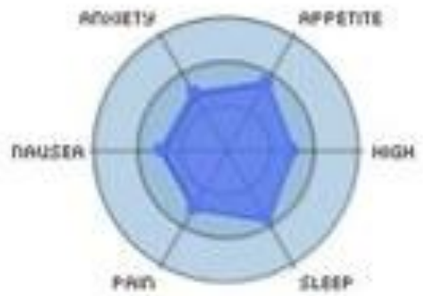
OG

Adjuster

THC: 12.80%
CBD: 0.50%
CBN: 0.77%

3 days ago

BudGenius Strain ID: BG0010001E839



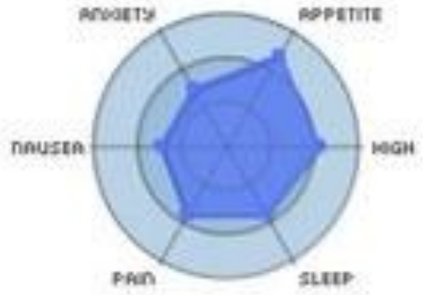
Platinum Kush

C.A.R.E. Alternative Meds

THC: 16.00%
CBD: 0.25%
CBN: 0.88%

1 week ago

BudGenius Strain ID: BG0010001E83C



Da Vapors OG

Vapors

THC: 20.12%
CBD: 0.31%
CBN: 0.62%

1 week ago

BudGenius Strain ID: BG0010001E81E

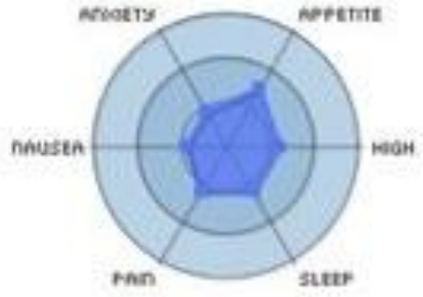
Master Kush

SoCal PURE

THC: 9.43%
CBD: < 0.05%
CBN: 1.21%

3 weeks ago

BudGenius Strain ID: BG0010001E811



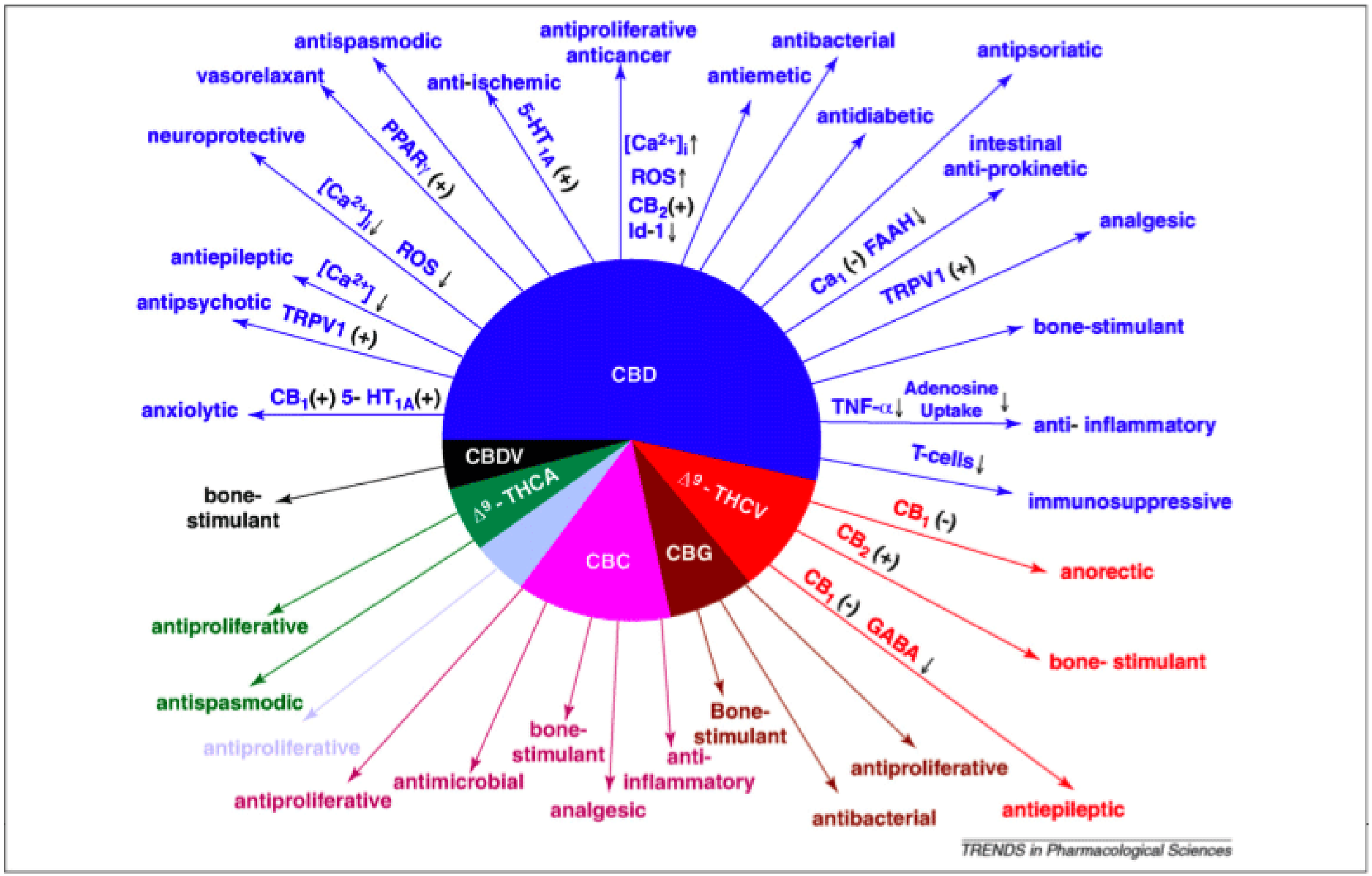


Figure 1. Pharmacological actions of non-psychotropic cannabinoids (with the indication of the proposed mechanisms of action).
Abbreviations: Δ^9-THC, Δ^9-tetrahydrocannabinol; Δ^8-THC, Δ^8-tetrahydrocannabinol; CBN, cannabinol; CBD, cannabidiol; Δ^9-THCV, Δ^9-tetrahydrocannabivarin; CBC, cannabichromene; CBG, cannabigerol; Δ^9-THCA, Δ^9-tetrahydrocannabinolic acid; CBDA, cannabidiolic acid; TRPV1, transient receptor potential vanilloid type 1; PPARγ, peroxisome proliferator-activated receptor γ; ROS, reactive oxygen species; 5-HT_{1A}, 5-hydroxytryptamine receptor subtype 1A; FAAH, fatty acid amide hydrolase.
(+), direct or indirect activation; ↑, increase; ↓, decrease.

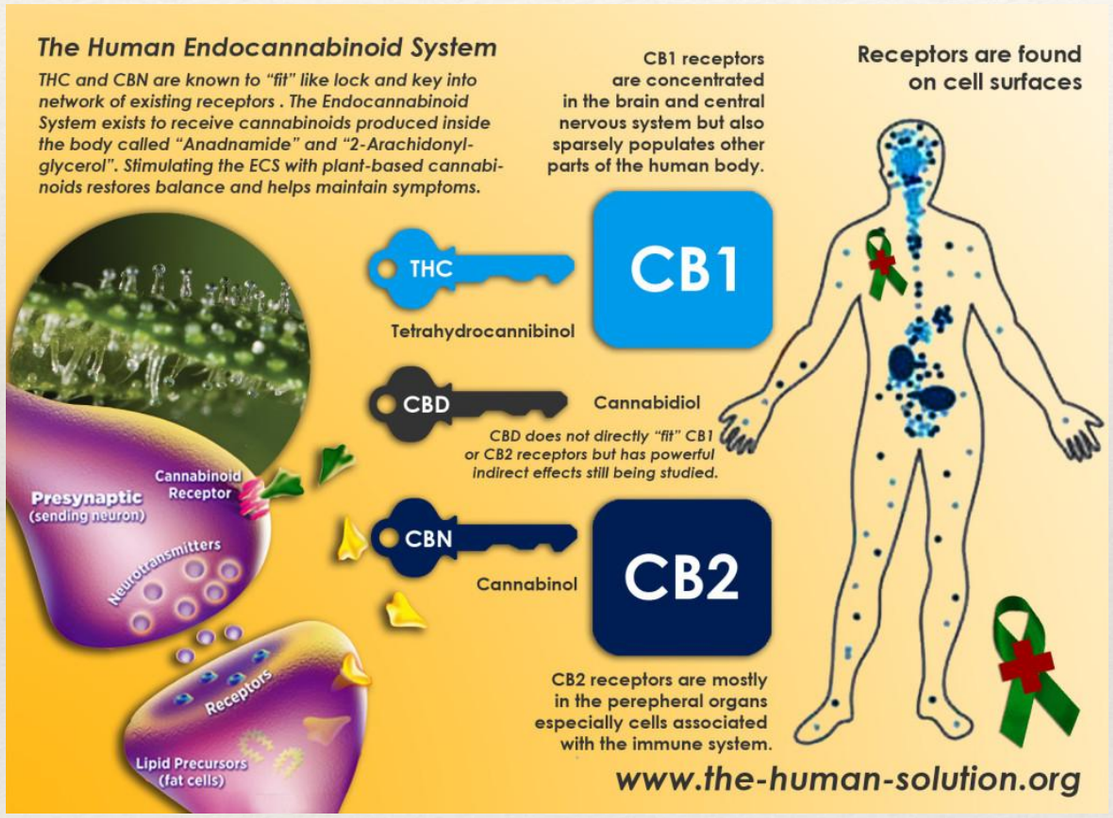
Consequences of Marijuana Abuse

- **Acute (present during intoxication)**
  - Impairs short-term memory
  - Impairs attention, judgment, and other cognitive functions
  - Impairs coordination and balance
  - Increases heart rate
  - Psychotic episodes
- **Persistent (lasting longer than intoxication, but may not be permanent)**
  - Impairs memory and learning skills
  - Sleep impairment
- **Long-term (cumulative effects of chronic abuse)**
  - Can lead to addiction
  - Increases risk of chronic cough, bronchitis
  - Increases risk of schizophrenia in vulnerable individuals
  - May increase risk of anxiety, depression, and amotivational syndrome*

1- Risk of Addiction

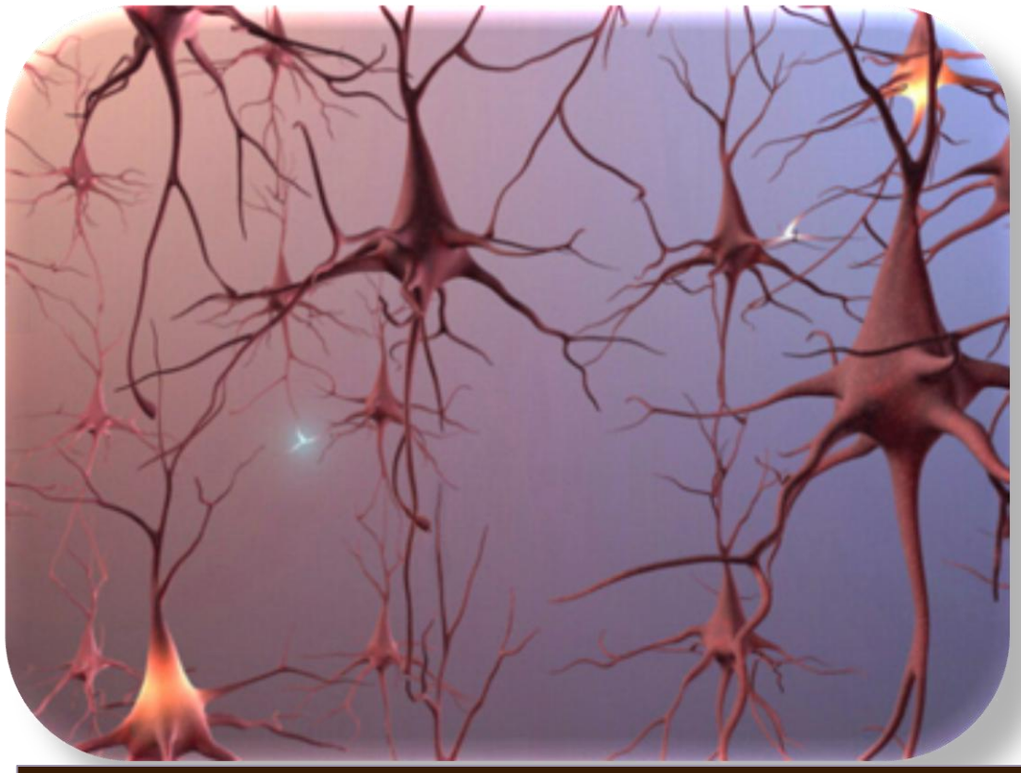
- 9% of experimenters will meet dependence criteria (2.7 million)
- 16% in those who start as teens (2-4x as likely to be dependent within 2 years of first use)
- 25-50% in daily smokers

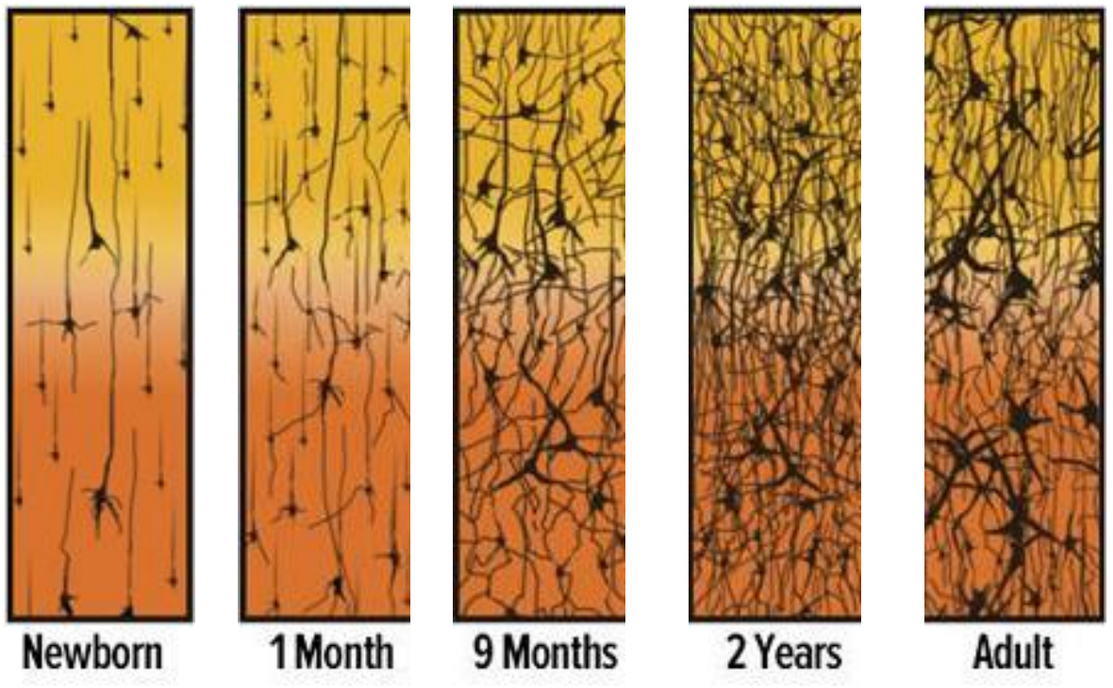
2- Marijuana and Brain Development



- The endocannabinoid system (ECS) has been detected from the earliest embryonal stages and throughout pre- and postnatal development; endocannabinoids, notably are also present in maternal milk

Endocanabinoids During Prenatal Brain Development





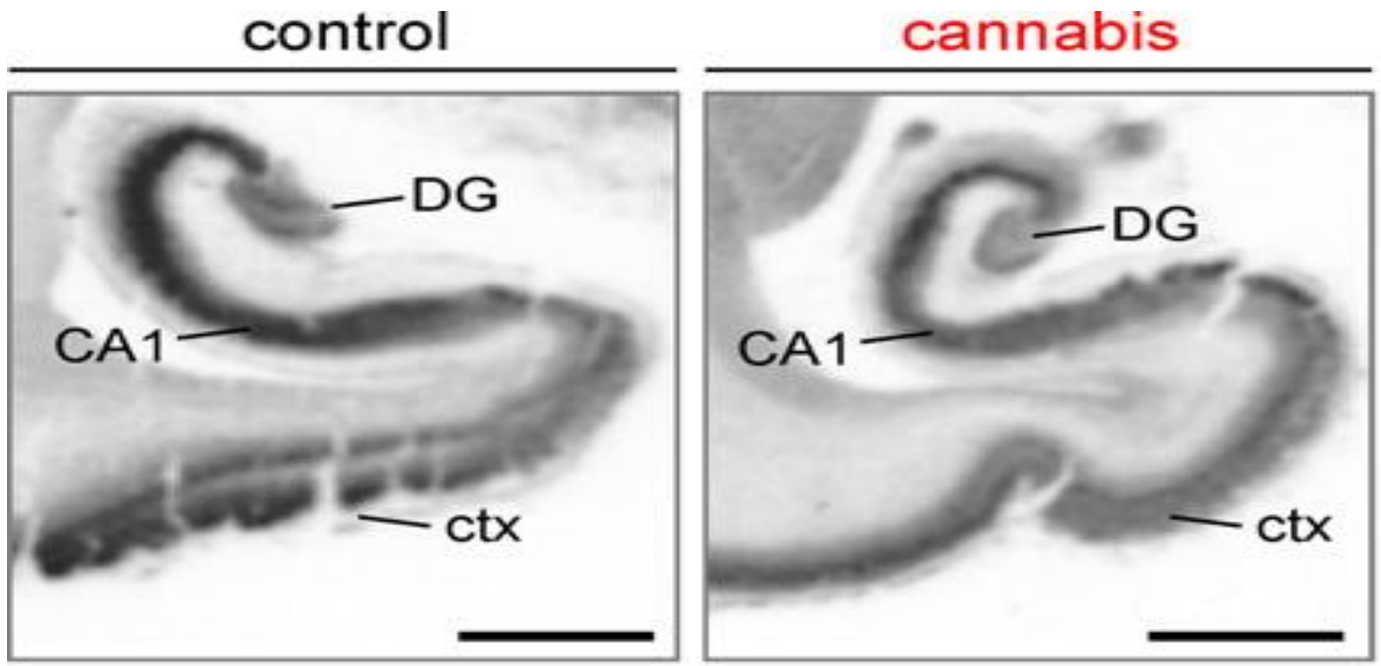
Cannabinoids in brain are implicated in brain development:

- **promote birth of new brain cells**
- **tell cells what type to become**
- **guide them to their targets**
- **help them form connections**

The Endocannabinoid System During Development

- Perinatal manipulation of the endocannabinoid system, by administering cannabinoids or by maternal marijuana consumption, **alters neurotransmitter and behavioral functions in the offspring**. Interestingly, the consequences of prenatal cannabinoids are similar to many effects of prenatal stress

Miswiring the brain: THC disrupts cortex development in fetus (Tortoriello et al., The EMBO J 2014)

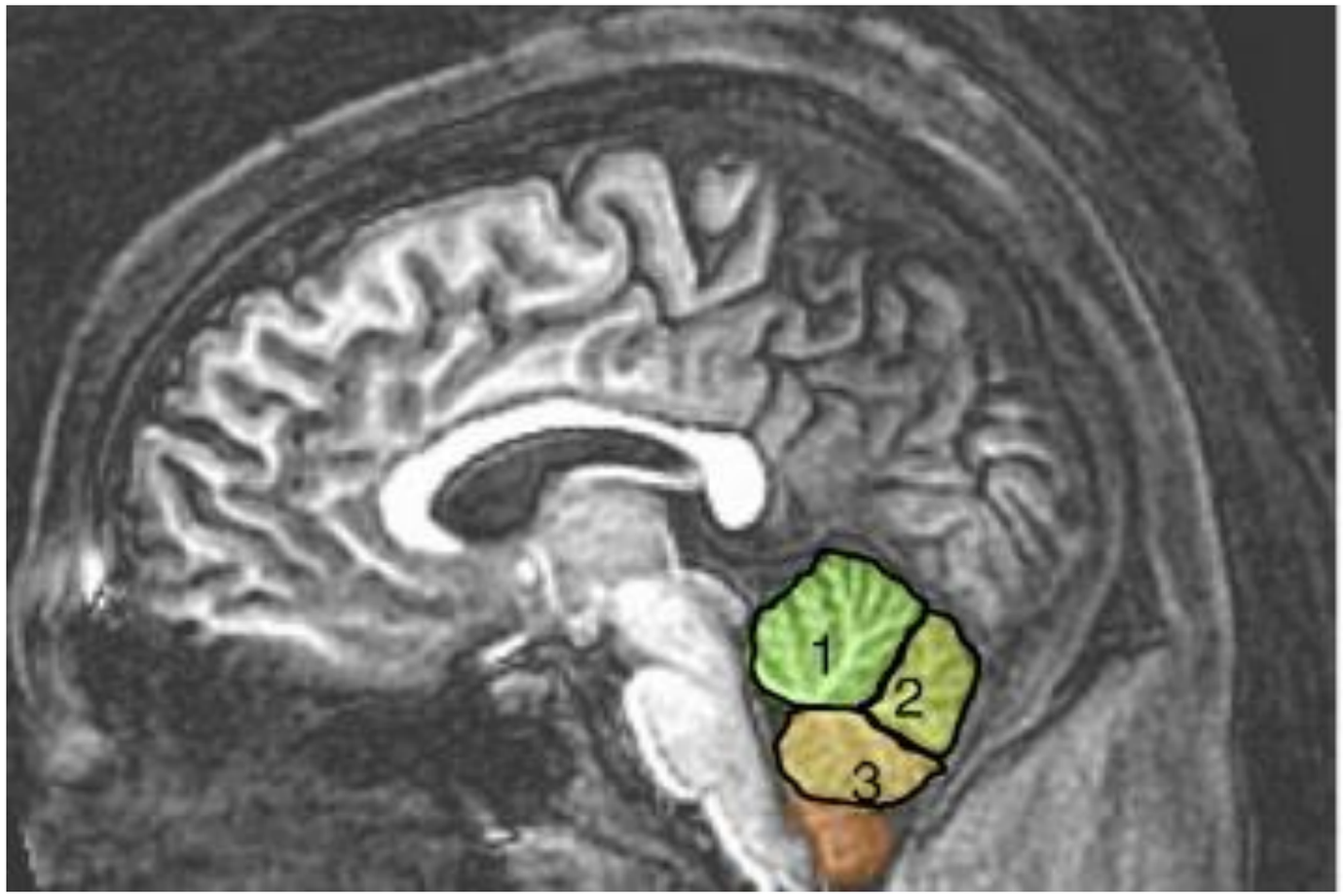


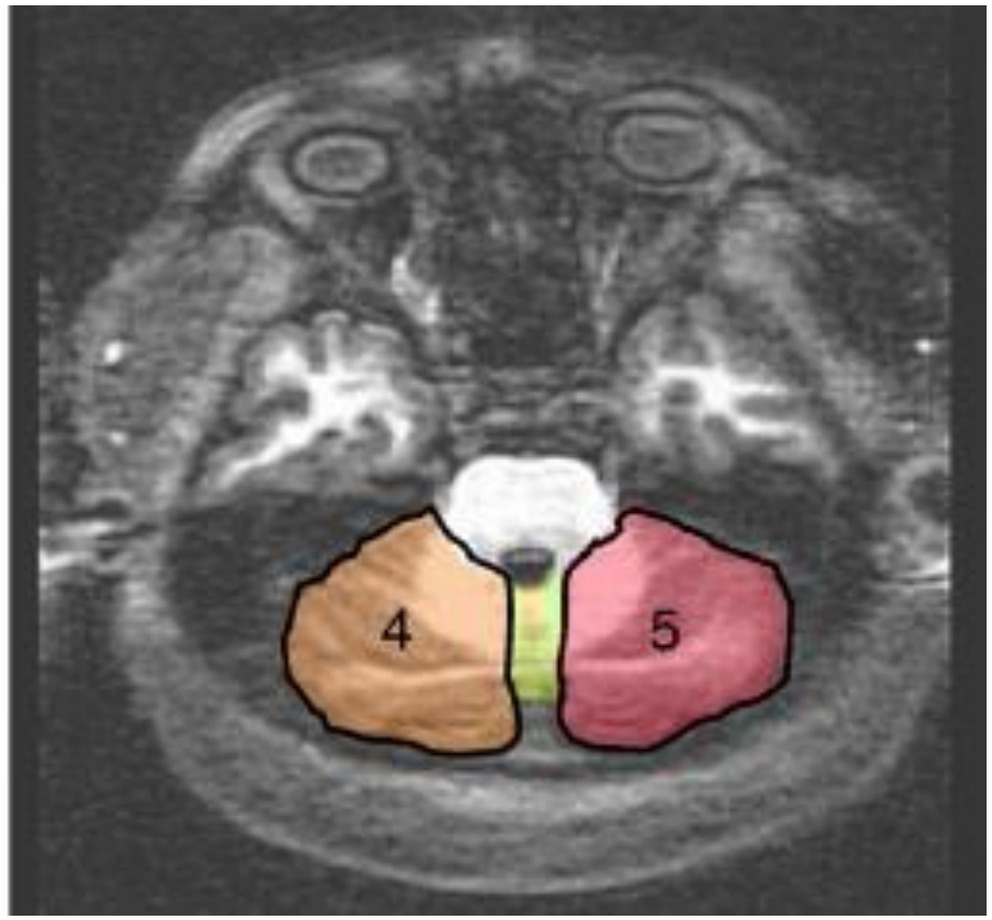
- THC reorganizes wires in the developing and adult nervous systems (Kano et al, 2009, Keimpema et al, 2010).
- THC impacts cortical wiring in the fetal cerebrum.
- THC disrupts development and maintenance of connections critical for highly ordered executive and cognitive functions (Kittler et al, 2000).

3.Effects of Marijuana on the brain of adolescents

- The cerebellum plays a role in balance, psychomotor speed, language generation, rhythm production, inhibition, attention, and memory

Adolescent Marijuana Users Have Enlarged Brain Cerebellum: Association with Poor Executive Function





Following one month of abstinence, adolescent MJ users had significantly larger posterior cerebellar vermis volumes than non-using controls. These greater volumes are associated with poorer executive functioning. Longitudinal studies are needed to examine typical cerebellar development during adolescence and the influence of marijuana use. MJ users had significantly poorer sustained attention, cognitive inhibition, and abstract reasoning

Source: Medina KL, Nagel BJ, Taper SF. Abnormal cerebellar morphometry in abstinent adolescent marijuana users. Psychiatry Research: Neuroimaging 182: 152-159, 2010.

4. Marijuana and cognitive function in adolescents

- 1,037 individuals were followed from birth to age 38.
- The adolescent MUO demonstrated a drop in their IQ (quotient of intelligence)from childhood “average” to adult “low-average” full-scale IQ. Indeed, the adolescent MUO individuals never achieved their predicted trajectory in IQ, even with sustained abstinence in adulthood
- (Meier et al., 2012).

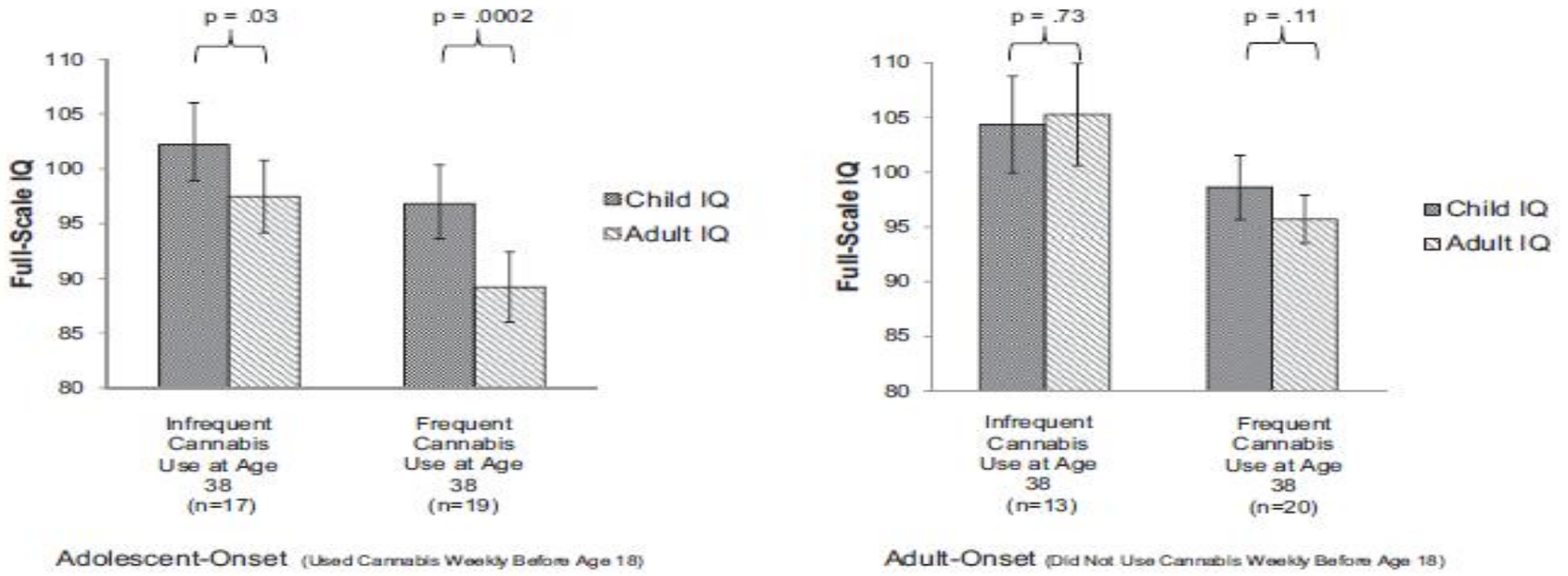


Fig. 3. Postcessation IQ among former persistent cannabis users. This figure is restricted to persistent cannabis users, defined as study members with two or more diagnoses of cannabis dependence. Shown is full-scale IQ in childhood and adulthood. IQ is plotted as a function of (*i*) age of onset of at least weekly cannabis use and (*ii*) the frequency of cannabis use at age 38 y. Infrequent use was defined as weekly or less frequent use in the year preceding testing at age 38 y. Median use among infrequent and frequent adolescent-onset cannabis users was 14 (range: 0–52) and 365 (range: 100–365) d, respectively. Median use among infrequent and frequent adult-onset cannabis users was 6 (range: 0–52) and 365 (range: 100–365) d, respectively. IQ decline was apparent even after cessation of cannabis use for adolescent-onset former persistent cannabis users. Error bars = SEs.

School Performance and Lifetime Achievement

- 6.5% of 12th graders use (higher in dropout population)
- Snowball effect, with one failure leading to many

5- Marijuana and mood

- The acute response to cannabis generally includes euphoria and feelings of detachment and relaxation
- Continuous smoking is associated with a gradual waning of the positive mood and social facilitating effects of marijuana and an increase in irritability, depression, social isolation, and low motivation
- Not all marijuana users experience it (~21%)
- Those with mental illness more likely to have the negative consequences

6- Marijuana and Psychosis

- Marijuana experience might trigger latent psychopathology of many types.
- There is reasonable evidence that heavy cannabis use, and perhaps acute use in sensitive individuals, can produce an acute psychosis (Paranoia)
- Scientific literature indicates general agreement that heavy marijuana use can precipitate schizophrenic episodes but not that marijuana use can cause the underlying psychotic disorder

7. Marijuana and Performance

- Acutely administered marijuana impairs cognition
- Longer term cognitive deficits in heavy marijuana users have also been reported
- A study of experienced airplane pilots showed that even 24 hours after a single marijuana cigarette their performance on flight simulator tests was impaired

8. Amotivational Syndrome

- Young people who drop out of social activities and show little interest in school, work, or other goal-directed activity
- No convincing data demonstrate however a causal relationship between marijuana smoking and these behavioral characteristics

Marijuana as a Treatment of Mental Illness?

- Some individuals report that marijuana “dulls anxiety or negative feelings”. Using marijuana to treat mood disorders was described in medical writings in the 19th and early 20th.
- Marijuana dulls dulls energy and motivation. Activation and engagement are key parts of recovery from depression.

Medical Marijuana

- The accumulated data indicate a potential therapeutic value for cannabinoid drugs, particularly for symptoms such as pain relief, control of nausea and vomiting, and appetite stimulation
- The effects of cannabinoids on the symptoms studied are generally modest, and in most cases there are more effective medications.
- The data on the adverse effects of marijuana are more extensive than the data on its effectiveness
- Clinical studies of marijuana are difficult to conduct
- The medical use of marijuana are not based on particular diseases but on symptoms

1. Marijuana and Pain

- There have not been extensive clinical studies of the analgesic potency of cannabinoids, but the available evidence from animal and human studies indicates that cannabinoids can have a substantial analgesic effect.
- No data on whether the effect is sustained or not
- Not convincing evidence that marijuana relieves migraine headaches

2. Marijuana and Immunosuppression

- THC have immunosuppressive effects which may by beneficial or detrimental
- Mice pretreated with THC one day before infection with a sublethal dose of the pneumonia-causing bacteria and then treated again one day after the infection with THC developed symptoms of septic shock and died; control mice that were not pretreated with THC became immune to repeated infection and survived the bacterial challenge. These mice failed to develop immune memory
- Little is known about the immune effects of chronic low- dose exposure to cannabinoids

Klein TW, Newton C, Friedman H. 1994. Resistance to Legionella pneumophila suppressed by the marijuana component, tetrahydrocannabinol. Journal of Infectious Diseases 169:1177—1179.

2. Nausea and Vomiting

- Cannabinoids are mildly effective in preventing emesis in some patients who are receiving cancer chemotherapy
- In a study comparing THC with metoclopramide, all patients received the same dose of cisplatin and were randomly assigned to the THC group or the metoclopramide group.
  - Results: Complete control of emesis occurred in 47% of those treated with metoclopramide and 13% of those treated with THC.
- In 1985, the FDA approved THC in the form of **dronabinol** for this treatment of nausea and vomiting associated with chemotherapy
- **Nabilone (Cesamet) and levonantradol** were tested in various settings; the results were similar to those with THC. As in the THC trials, nabilone and levonantradol reduced emesis but not as well as other available agents

Gralla RJ, Tyson LB, Borden LB, et al. 1984. Antiemetic therapy: A review of recent studies and a report of a random assignment trial comparing metoclopramide with delta-9-tetrahydrocannabinol. CancerTreatment Reports 68:163—172.

3. Appetite Stimulation

- In 1992, the FDA approved THC, under the trade name Marinol (dronabinol), as an appetite stimulant for the treatment of AIDS-related weight loss
- Dronabinol was associated with an increase in appetite and stable weight, in patients with wasting syndrome associated with AIDS
- The profile of cannabinoid drug effects suggests that they are promising for treating wasting syndrome in AIDS patients.

4. Reproductive System

- In both male and female animals and humans, THC injections suppress reproductive hormones and behavior
- Injections of THC result in rapid, dose-dependent suppression of sex hormones and embryo implantation appears to be inhibited.
- The animal and human studies are based on acute treatments (single injections) or short term treatments

5. Multiple Sclerosis

- There are numerous anecdotal reports that marijuana can relieve the spasticity associated with multiple sclerosis or spinal cord injury
- Carefully designed clinical trials testing the effects of cannabinoids on muscle spasticity should be considered

Charlotte’s Web

- A few years ago, Charlotte's doctors were out of ideas to help her. Suffering from a rare disorder known as Dravet’s syndrome, Charlotte had as many as 300 grand mal seizures a week, was confined to a wheelchair, went into repeated cardiac arrest and could barely speak. Now Charlotte is largely seizure-free, able to walk, talk and feed herself, with her parents attributing her dramatic improvement to this strain of medical cannabis.

6. Epilepsy

- Studies in animal models have shows CBD works as an anticonvulsant
- A new international, multi-center study led by researchers from UCSF Benioff Children's Hospital is the first to evaluate whether purified cannabinoid is effective in treating severe forms of childhood epilepsy that do not respond to standard antiepileptic drugs
- The drug, called Epidiolex, is a purified cannabinoid that comes in a liquid form containing no tetrahydrocannabinol (THC)

7. Marijuana and Lung Diseases

- Marijuana smoking is associated with abnormalities of cells lining the human respiratory tract.
- Numerous studies suggest that marijuana smoke is an important risk factor in the development of respiratory disease mainly bronchitis.

Is Marijuana Smoke "Cleaner" Than Tobacco Smoke?

Marijuana smoke: 20 X ammonia levels than tobacco smoke

Marijuana smoke: more hydrogen cyanide than tobacco

Marijuana smoke: more tar, benzene, toluene, cancer- causing hydrocarbons than tobacco smoke

Marijuana and cigarette smoke have known carcinogens, other chemicals implicated in lung diseases

Moir et al, A Comparison of Mainstream and Sidestream Marijuana and Tobacco Cigarette Smoke Produced under Two Machine Smoking Conditions. *Chem. Res. Toxicol.*, **2008**, *21* (2), pp 494–502

To summarize…

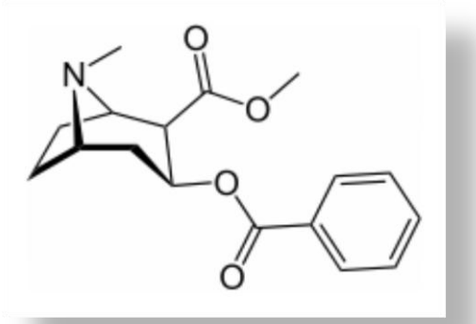
Table 2. Level of Confidence in the Evidence for Adverse Effects of Marijuana on Health and Well-Being.

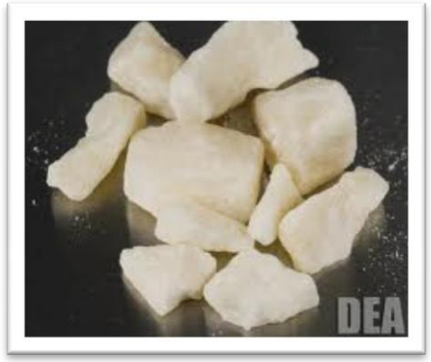
Effect	Overall Level of Confidence*
Addiction to marijuana and other substances	High
Abnormal brain development	Medium
Progression to use of other drugs	Medium
Schizophrenia	Medium
Depression or anxiety	Medium
Diminished lifetime achievement	High
Motor vehicle accidents	High
Symptoms of chronic bronchitis	High
Lung cancer	Low

* The indicated overall level of confidence in the association between marijuana use and the listed effects represents an attempt to rank the strength of the current evidence, especially with regard to heavy or long-term use and use that starts in adolescence.

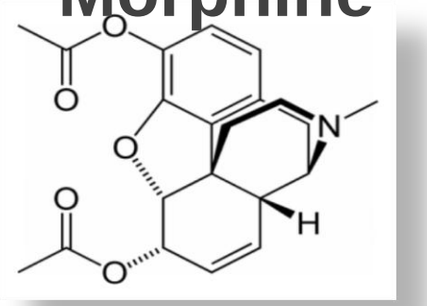
Psychoactive Plants Also Produce Medications

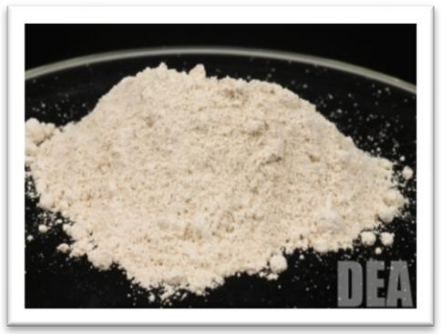
Cocaine



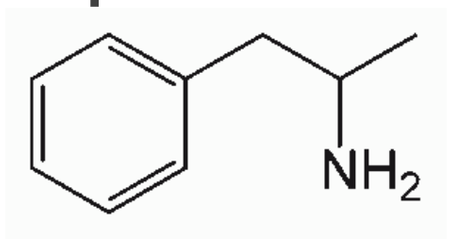


Morphine

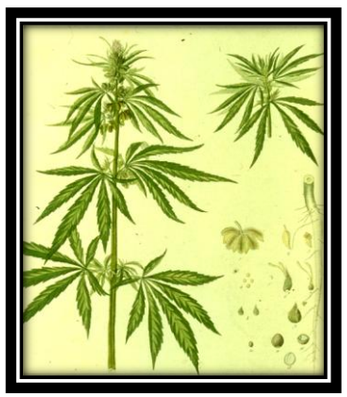


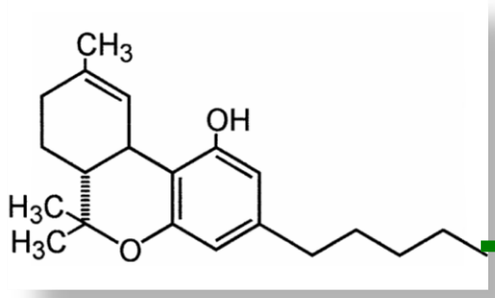


Amphetamine



Δ-9-tetrahydrocannabinol (THC)





Why not FDA approved?

- Scientific evidence to date is not sufficient for the marijuana plant to gain FDA approval, for two main reasons.
  - Not enough clinical trials as its difficult to get approved.
  - A substance must have well-defined and measureable ingredients that are consistent from one unit (such as a pill or injection) to the next but cannabis has 100 of variable compounds with different action. Use of defined cannabinoids permits a more precise evaluation of their effects

- However, pure THC-based drugs are already FDA approved and prescribed
  - Dronabinol (Marinol®) and Nabilone (Cesamet®) for nausea and pain associated with cancer chemotherapy and stimulating appetite in patients with wasting syndrome.
  - Sativex for the relief of cancer-associated pain and spasticity and neuropathic pain in multiple sclerosis.

Thank you…